REMARKS

Applicants wish to thank Examiner Quang for his detailed commentary provided with the outstanding Advisory Action. While proposed amendments submitted with the after-final Response filed January 08, 2008 were entered, the Declaration of Dr. Neil Theise attached therewith was not considered nor entered by the Examiner. The present paper is being submitted, in part, so that the Examiner may enter and consider the Declaration in conjunction with the remarks made therein.

Status of the claims

Claim 1 is amended and claim 41 is newly added. Support for claim 41 may be found, at least, on page 6, lines 20-22. No claims have been canceled with this Response. Hence, claims 1, 3, 4, 6-9, 12-21, 23-34, and 41 will be pending and under active consideration.

Claim rejections under 35 U.S.C. § 103

Claims 1, 3, 4, 6-9, 12-21 and 23-34 stand rejected as allegedly being unpatentable over PCT Application No. WO 95/13697 to Reid *et al.* ("Reid") in view of U.S. Patent No. 6,129,911 to Faris ("Faris") and U.S. Patent No. 5,843,024 to Brasile ("Brasile") for the reasons of record. Applicants traverse this rejection on the following grounds.

None of the cited references, alone or in combination, teaches or suggests a method of isolating liver progenitor cells from a liver tissue obtained between about 2 hours and 30 hours postmortem.

In order to establish a *prima facie* case of obviousness, the Office must preliminarily establish that each and every claimed limitation may be found in the prior art. Applicants respectfully submit that the Examiner has failed to meet this threshold requirement. No reference in the art teaches or suggests a method of processing a non-fetal donor liver tissue or procuring liver progenitor cells from a liver tissue obtained between *about 2 hours and 30 hours postmortem*. At least with respect to the primary reference, the Examiner concedes this fact. Office Action, page 4, para. 1.

Indeed, the Examiner does not appear to contest the fact that *no* reference teaches or suggests a method of processing a non-fetal donor liver tissue or procuring liver progenitor cells from a liver tissue obtained between about 2 hours and 30 hours postmortem. Rather, the Examiner has opted to "cherry pick" choice, sweeping statements in the cited references and "derive[] from the totality of the combined teachings" a notion that the claimed invention would have been obvious to one or ordinary skill in the art at the time the present invention was filed.

For example, while Reid only teaches the isolation of liver cells from embryonic and neonatal livers *immediately* post-mortem, the Examiner notices that Reid professes that "the method of the invention offers a systematic approach to isolating hepatoblasts from any age from any species." Presumably, the Examiner interprets "any age" to include 2 hours and 30 hours after death. Similarly, despite the fact that Faris only teaches the isolation of cells *immediately* following anesthetization of the donor, the Examiner notices that Faris professes that the isolation method may be performed on "mammalian organ donors including deceased donors or cadavers." Finally, with respect to Brasile, notwithstanding its silence on stem cells altogether, because Brasile teaches the "resuscitation" of whole livers post-mortem, the Examiner presumably takes this teaching to imply that stem cells could also be isolated from the livers so "resuscitated."[1]

The fact remains, however, whether the references are taken alone or in combination, "[t]his invention was completely unexpected, since all known prior art references regarded ischemically damaged organs as being totally useless for any meaningful purpose" and that the present inventors were the first to take advantage of the discovery that progenitors were actually *resistant* to ischemia. [Specification, para. 0016.] This notion is further supported by the Declaration of Dr. Neil Thiese, being submitted herewith. Dr. Theise, who is an expert in hepatic stem cells, attests that at the time of invention, the idea that hepatic stem cells could be

[1] Applicants do not doubt the validilty of the claims issued with Brasile as suggested by the Examiner. Page 9, 1st para. of the Office Action. Rather, Applicants highlight that even if Brasile's resuscitation solution were to "reverse" impairment of liver *function*, there is no teaching or suggestion that functional liver progenitors *per se* can be isolated from these "impairment-reversed" livers."

isolated from livers greater than about 2 hours postmortem was met with "doubt, if not derision," by the majority. Declaration at 9-10.

There existed no reasonable expectation of success in modifying the references to arrive at the claimed invention.

Applicants respectfully submit that one of ordinary skill in the art would have had no reasonable expectation of success in modifying the teachings of Reid with Faris and Brasile as suggested by the Examiner. Simply put, the scientific community held this view because it assumed that the liver autolyzes within less than an hour, and that progenitor cells—being particularly sensitive to ischemic damage—would be the first cells to die. Dr. Theise confirms this prejudice and the Examiner's review of the literature to-date confirms this statement. Declaration at 10. Together, the evidence lends convincing weight to Applicants assertion that one skilled in the art would *not* have expected any success in isolating progenitor cells from tissue greater than about 2 hours postmortem.

In conclusion, Applicants submit respectfully that the rejection of claims 1, 3, 4, 6-9, 12-21 and 23-34 under 35 U.S.C. § 103 has been traversed, and Applicants request respectfully that the rejection of same claims be withdrawn.

Double patenting

Claims 1, 2-4, 8-9, 12-21 and 23-34 stand rejected for alleged non-statutory obviousness-type double patenting over claims 1-4 of USP No. 6,069,055 or claims 1-32 of USP No. 6,242,252 in view of Faris and Brasile. The Examiner's reasons for rejection are set forth on pages 11-13 and essentially reiterate the reasons for rejection under 35 U.S.C. § 103.[2] Applicants respectfully traverse this rejection. At least for the reasons expounded above in rebutting the Examiner's *prima facie* case for obviousness with the equivalent references, Applicants respectfully submit that the pending claims are not obvious over the cited patents.

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[2] The Reid reference, discussed hereinabove, is identical in disclosure to USP Nos. 6,069,005 and 6,242,252.

Applicants believe that the present application remains in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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